NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

66/CNECV/2012

NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

OPINION ON DRAFT BILLS No. 266/2012 AND No. 323/2012 ON CLINICAL RESEARCH AND CLINICAL TRIALS

(September 2012)

His Excellency the Minister of Health having requested, as a matter of urgency, the National Council of Ethics for the Life Sciences (CNECV) to issue Opinions on the Draft Bills, respectively no. 266/2012, which aims to regulate clinical research, and no. 323/2012, which aims to make the (second) amendment to Law 46/2004, which regulates clinical trials with medicinal products for human use, the CNECV presents the following Opinion.

1. It turns out, from the comparative study of its bills, that Draft Bill 266/2012 deals in fact with new material, while Draft Bill 323/2012 is intended primarily to harmonise the legal text currently in force (46/2004) with the legal system applicable to all clinical research, and which will be in force if the law based on Bill 266/2012 is approved. That is, the second bill is simply consequent to the eventual approval of the first bill, in the form of law. Therefore, it does not appear necessary to prepare two separate opinions, since the second Bill is covered by the evaluation that is made on the first.

The CNECV had the opportunity to issue previous Opinions on clinical trials – Opinion on the Clinical Evaluation of Drugs (4/CNECV/93) and Analysis Document – comparison of Legislation relating to clinical trials and Ethics Committees and Doctrine set forth by CNECV (13/CNECV/95), both available at www.cnecv.pt.

Also to be highlighted, at international level, the Convention on Human Rights and Biomedicine (Council of Europe), ratified on 3 January 2001 and in force in Portugal since 1 December 2001, and the Additional Protocol to the Convention on Human Rights and Biomedicine concerning biomedical research; the Charter of Fundamental Rights of the European Union, in particular its article 3; and the UNESCO Universal Declaration on Bioethics and Human Rights. Also, the Helsinki Declaration in its latest wording of 2008.

2. Clinical research obviously includes clinical studies and clinical trials of drugs. The importance and significance of this search for biological knowledge and truth and the extraordinary contribution that scientific advances have provided to human life is universally recognised, both in its quantitative parameter and in its quality. Nor does it call into question the social and economic benefits that such research brings. All these gains, in life, health, economy and social welfare would not, by themselves, justify resorting to human beings for experiments, whose risk can be estimated or calculated, but never fully anticipated. In addition to a classical utilitarian criterion (clinical research results in a very appreciable good to a large number of people), one must use other criteria of ethical reasoning.

3. In this regard, and bearing in mind that the progress achieved by the clinical studies and trials cannot be achieved solely by other means (particularly in the pre-clinical stage, by experiments on animals, tissues, cell cultures, purely physicochemical methods), the lawfulness of those studies and trials is established, since the values of solidarity and altruism point out how crucial it is to achieve enormous benefits for the health of patients, for individual members of the community or for the community as a whole, through the voluntary and conscious participation of a few in such studies and trials.

4. Being not only lawful but also ethically irrecusable to obey this imperative, it is essential that the scientific activity is accomplished within a legal framework that guarantees its appropriateness, quality and relevance, and above all protects the human rights of persons who are subjects or (as said in the bills under consideration) participants in such studies and trials. In fact, the physical and psychological integrity, as well as the dignity of the participants, must be guaranteed, not to mention the supreme good that is life. That is a concern expressed within the Draft Bills under consideration in the various chapters that comprise them, which is to be commended. These Bills are aimed in this direction by outlining the framework of regulatory interventions, the conditions for the approval of projects or protocols, surveillance and monitoring of their implementation, reliable registration of all research data and (conditioned) access of other scientists to such data.

At the same time, the authorities should recognise that the community should be informed in a transparent way on aspects of the research related, among other factors, to risks, benefits or results, which may be both positive and negative.

5. It does not seem, therefore, that there are serious or substantial ethical objections or reservations. Even so, we would point out the vagueness or ambiguity, in addition to the wording that is sometimes less fortunate, which can be easily detected in the text. It seems clear that this observation has ethical support, because it would be a serious matter if, in future application, there should occur deviations, at the level of *praxis*, undesirable or harmful to the participants, due to a deviant interpretation of the intentions of the legislator. We refer to what are deemed to be the main weaknesses in this area:

5.1. Article 2(a) and (b) of Draft Bill 266/2012; article 2(t), (v) and (x) of the Annex to Draft Bill 323/2012 – an incomplete definition of ‘adverse event’, which in fact is confused with ‘adverse reaction’;

5.2. Article 2(h) of Draft Bill 266/2012; article 2 of Draft Bill 323/2012, in the amendment to article 2(o) of Law no. 46/2004 of 19 August – the present bioethical reflection prefers the

contemporary expression of 'informed consent' (instead of the bill's: 'free consent'), that is 'taken freely'; refers to the meaning of consent to be given by the participant in the trials, set down in article 14 of the Additional Protocol to the Convention on Human Rights and Biomedicine concerning biomedical research, and is qualified as 'informed, free, express, specific and documented', revocable at any time.

5.3. Article 2(q) of Draft Bill 266/2012 – the ambiguity of the definition of 'researcher', a definition that, in that paragraph, does not adequately address the difference between the status of 'main researcher' and that of 'researcher'. On the other hand, since the research may lead to the presence of researchers who are not directly health professionals[1] (for example, biologists, biochemists, among others), it would be advisable to determine with more precision the professional and scientific qualifications of the main researcher. Remember though that, in the team of researchers, the responsibility for providing care to the participants in the research belongs to a doctor or to whoever is legally qualified to do so.

It is also important to define more precisely the specific qualifications of the researcher *in a clinical trial* and, on the other hand, the researcher *in a clinical research* that does not presuppose carrying out a trial.

5.4. Article 2(s) of Draft Bill 266/2012 – there is the same uncertainty about the status of the 'monitor'. Indeed, if clinical research involves the continued contact with patients or participants, then the terms under which this contact must be made by a health professional should be indicated.

5.5. Article 2(x) of Draft Bill 266/2012 – a reference to 'unauthorised experimental intervention' (*sic*) – should never occur in an intervention of this type;

5.6. Article 5(1) of Draft Bill 266/2012, article 5(1) of the Annex to Draft Bill 323/2012 – the inclusion of 'other participants, current or future' as potential beneficiaries of the results of a study, when it probably would have been for the benefit of other people, not participants in the study in question.

5.7. Article 12 (Clinical Study Centre) should certainly mention that among the competencies of the Centre is that to accept carrying out the study or not; if it were not so, the Centre would be required to allow, within its walls, any proposed study by any sponsor, which is absurd.

[1] In this Opinion, the term 'health professionals' is reserved for professionals who provide health care or treatment.

6. More important are some flaws detected in Chapter II of Draft Bill 266/2012, which deals with 'Clinical study participants'.

6.1. Here are listed the minimum conditions for such participation to take place; the requirement that the competent Ethics Committee (CEC) could dispense with some of these conditions is incomprehensible (and should be deleted).

6.2. It is also noted that the principle of gratuitousness (prohibition of material benefit to the participants) is referred to in sections relating to minors and disabled people, but is wrongly omitted in Article 6 (concerning adults capable of giving consent).

6.3 Moreover, the principle that the withdrawal of consent may not affect treatment or ongoing care or in future should be reinforced, under penalty of possible coercion of the will of vulnerable participants.

6.4. In this context, it should also be corrected the statement that 'the right to health should be ensured'; this is never possible, given the unpredictability that is a constant in experiments with living beings; what must be ensured is that all foreseeable risks are excluded, thus achieving integrity.

7. The clinical trial against a placebo must be limited to situations where there are no alternatives, favouring the trial as opposed to known therapies and recognized as effective, the only way to ascertain the true therapeutic innovation that the new drug brings.

8. The Draft Bill is silent on the subject that concerns the 'declaration of conflicts of interest' on the part of the sponsors or health professionals involved in clinical trials. However, by virtue of the transparency that should guide the overall process of these trials when they involve public resources, financial or other, it is recommended that the law be explicit regarding the need for this 'declaration of conflict of interest', where appropriate.

Once this principle is accepted, there are still several specific issues, namely the specificity of the content of this declaration, the entity or entities to which the declaration should be delivered (for example, not only the institution where the trial takes place, but also its dissemination through Internet sites under the responsibility of the competent Ethics Committee, hopefully in conjunction with the competent authorities at Community level). The procedures for access to consultation should also be implemented, that is, the conditions governing the free access to consultation, in particular on the part of the trial participants.

This measure will enhance the transparency of conditions surrounding clinical trials, as well as the informed consent freely given by participants, which also implies the possibility of abandoning the trial when they so wish, thus resisting any undue pressure to remain in the trial against their will.

One must add, however, that in no way, the conflict of interest declaration may intervene as strictly scientific evaluation criterion of clinical trials.

9. The Bills contain an extensive list of articles of administrative and organizational nature, which is less susceptible to ethical evaluation. In any case, it should be noted that:

9.1. From the ethical point of view, it may be considered advisable to harmonise into a single Law the Draft Bills no. 266 and no. 323, and with these Law no. 46/2004 of 19 August, so as to avoid possible negative effects resulting from a duplication of laws.

9.2. The complex and centralising system proposed seems cumbersome, not immune to bureaucratization and difficult to coordinate so that all efforts and interventions are for the common good.

9.3. The establishment of the *National Ethics Committee for Clinical Research* (CEIC) as a super ethics committee does not sufficiently respect the specific competencies of the Health *Ethics Committees* (CES), as these competencies are far from being limited to the issue of clinical research and clinical trials.

9.4. Clinical research without direct intervention on the participants should be left to the sole responsibility of the local CES – as is the case with epidemiological research, namely the observational studies.

9.5. With regard to the proposed establishment of a National Network of Health Ethics Committees, pursuant to what is set forth in article 29 of Draft Bill 266, by virtue of the proposed objectives and the consequences that the creation of such a network entails, it is ethically necessary and urgent to tackle this issue in the context of a possible revision of Decree-Law No. 97/95 of 10 May, which regulates the health ethics committees.

In any event, it is advisable to avoid creating a superstructure or body that decreases or impairs the independence of the CES.

9.6. The creation of an Ethics Committee in all public or private research centres, whether or not integrated in institutions of higher education, is also recommended.

9.7. In order to avoid multiple legal documents relating to identical or very similar issues, the creation of a single law covering matters relating to Law no. 46/2004, as well as the Draft Bills no. 266/2012 and no. 323/2012, is recommended.

10. In conclusion, no global ethical objections are found. It is understood, however, that the Draft Bills in question can and should be corrected and improved, taking into account the various aspects mentioned above.

Lisbon, 21 September 2012

The President,
Miguel Oliveira da Silva

The present Opinion was approved in the plenary meeting of 21 September 2012. Besides the President, the following Counsellors were present:

Michel Renaud (rapporteur); Francisco Carvalho Guerra (rapporteur); Ana Sofia Carvalho; Carolino Monteiro; Isabel Santos; José Germano de Sousa; Lucília Nunes; Maria de Sousa; Pedro Nunes; Rosalvo Almeida.

The CNECV decided to ask Professor Walter Osswald, Professor Emeritus of the Faculty of Medicine of Oporto, for a preparatory study that served to support the work of the rapporteurs in this Opinion.